

A Test for Myocardial Infarction

The Present Status of the Use of Serum Lactic Acid Dehydrogenase

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In 1954 and 1955 Hill and Levi and other investigators reported the serum content of the enzyme *lactic acid dehydrogenase* (LDH) to be elevated in neoplastic diseases. They studied 51 patients with cancer.^{1,2} This enzyme was also shown to be increased in the serum of patients with myocardial infarction.^{6,8} Further reports have tended to emphasize the value of this test in myocardial infarction⁷ and perhaps in liver disease, and to minimize its value in cancer detection.^{4,9} Our own observations are here reported as another fragment of knowledge regarding the uses of this test.

METHODS

Serum lactic acid dehydrogenase determinations were done according to the method of Hill and Levi.² Blood was drawn with special care to avoid hemolysis. The serum was separated from the specimen within one hour after collection, centrifuged until no blood cell sediment could be observed macroscopically and then centrifuged a final time. The specimens of serum were stored frozen in Wassermann tubes in amounts to be diluted for the test procedure. Determinations were done in duplicate on all specimens on two successive days. The determinations were made in a Beckman Model B Spectrophotometer at a wave length of 340 millimicrons using 1 cm.² cuvettes. The LDH activity was determined in units of optical density change. One unit is equal to an optical density change of 1.00 per ml. per 30 minutes at 38°C. in a substrate pH of 7.8. The substrate was prepared according to the method of Hill and Levi.² All solutions except the buffer were prepared fresh each day.

The following clinical groups were tested: 30 patients with carcinoma, 23 with myocardial infarction, 11 with liver disease, 47 with miscellaneous illnesses, 11 with infectious mononucleosis and 39 with uncomplicated pregnancy. All patients with myocardial infarction had electrocardiographic evidence in support of this diagnosis. Three died and in two the diagnosis was proved by autopsy. In the patients with cancer the lesions were localized in four instances and disseminated in 16, five had

• Determination of the amount of lactic acid dehydrogenase in the blood has been demonstrated as a useful aid in the diagnosis of myocardial necrosis. The reliability of the test and the time element of the appearance and disappearance of the enzyme in the blood give it advantages over transaminase determinations. In addition there appears to be a correlation of lactic acid dehydrogenase content with metastatic carcinoma. The levels of the substance correlate with the presence or absence of metastatic lesions and also with the extent of the metastasis. Few other clinical states are associated with increased levels of this enzyme, and in most instances the few that are can be excluded by other reliable criteria.

leukemia and five had unclassified malignant disease. The diagnosis of infectious mononucleosis was established by a significant heterophil titer or a rise in titer in two or more specimens. The normal range was established by test of 268 patients showing no evidence of clinical disease.

RESULTS

Comparison of the various groups evaluated (Table 1) showed lactic acid dehydrogenase to be always elevated in myocardial infarction, and high values were obtained as late as two weeks after the

TABLE 1.—Comparison of Lactic Acid Dehydrogenase Values in Patients with Various Diseases and Normal Persons

Clinical State	No. of Cases	No. of Tests	LDH Units	
			Mean	Range
Carcinoma:				
Disseminated.....	21	22	25.5	16 to 80
Localized and unclassified.....	9	11	14.0	9 to 19
Myocardial infarcts.	23	27	25.5	10 to 65
Liver disease.....	11	13	15.0	7 to 19
Infectious mononucleosis.....	11	14	19.25	14 to 57.0
Uncomplicated pregnancy.....	39	42	9.5	7.5 to 13*
Miscellaneous:				
Infections.....	15	15	10.0	7.5 to 12.0
Others.....	32	36	10.0	7.0 to 44.0†
Normals.....	268	320	10.0	7.5 to 12.5

Standard Deviation = 0.88, Range: 8.3 to 11.8.

*1 case—13 units. †4 cases—above 13 units, terminal.

The Clinical Laboratory of San Bernardino.
Submitted November 13, 1957.

attack. In metastatic carcinoma the LDH content was consistently high, with the extreme elevations usually associated with leukemia. Patients with liver disease showed the least striking variations in serum lactic dehydrogenase and oftentimes normal levels were obtained in the absence of jaundice (Table 2). In cases of infectious mononucleosis the LDH determinations were consistently high and appeared to vary directly with the heterophil titer. Levels in uncomplicated pregnancy were within normal limits, as observed by Hill³ subsequent to his initial report of elevated levels and in agreement with the work of McDonald.⁵

DISCUSSION

The usefulness of lactic acid dehydrogenase determinations in myocardial infarction seems well established. There has been a total of at least 118 cases reported in the literature since the original observation made by Wroblewski and LaDue.⁸ It has been pointed out in recent articles by White⁷ and McDonald⁵ that elevated serum values of this

enzyme may be present at least a week following infarction. This sets the lactic dehydrogenase determination above the transaminase determination as a guide to the presence or absence of myocardial necrosis.

In liver disease there is obviously great need for further study of the associated presence of this enzyme in the serum. There have been 22 cases of hepatitis and 40 cases of cirrhosis reported, not including Wroblewski's. It appears that a certain proportion of patients with liver disease, particularly those with active hepatitis in the presence of jaundice, have an elevation of this enzyme in the serum. However, the relationship of the appearance of this enzyme to changes in the serum proteins has not been well worked out and the role of some degree of hepatic cell necrosis has not been determined. This would seem to be a good field for further clinical and laboratory observation.

The controversial problems surrounding the development of the so-called "cancer test" are well illustrated in these studies. Determination of ele-

TABLE 2.—Comparative Laboratory Values for Various Tests in Liver Disease

Case No.	LDH* Units	Cephalin Flocculation	Total Bilirubin mg. per 100 cc. Serum	Serum Proteins† (Per Cent of Total)				
				Albumin	Alpha ¹	Alpha ²	Beta	Gamma
1.....	12.0	3+	45	6	8	20	21
2.....	7.0	4+	53	5	10	14	18
3.....	15.0
4.....	16.5	4+
5.....	17.5	4+	3.8	45	7	11	7	30
6.....	19.0	4+
7.....	16.0
8.....	12.0
9.....	16.5	4+
10.....	9.0	4+	3.9	39	6	8	18	29
11.....	9.5	4+	2.4	36	5	10	17	32

*Lactic acid dehydrogenase.

†Normal range of serum proteins: Albumin—50 to 55%; Globulins: Alpha¹—4 to 7%; Alpha²—7 to 11%; Beta—11 to 15%; Gamma—16 to 18%.

TABLE 3.—Lactic Acid Dehydrogenase Values in Carcinoma as Reported by Various Investigators, 1954-1955

Report	Units	Patients with Carcinoma			Controls		
		No.	Mean	Range	No.	Mean	Range
Hill, B., et. al.....	O.D.* change in 30 minutes per 0.01 cc. serum	51	0.21	0.110 to 0.670	104	0.085	0.049 to 0.110
Zimmerman†.....	Micro-mols of DNPH‡ per 100 cc. serum in 30 minutes	30	50 per cent of patients were elevated	100 to 800	40 Normal	181	80 to 250
Hill, J. H.....	O.D. change in 30 minutes per 0.01 cc. serum	87	0.149	0.060 to 0.583	309	0.143	0.048 to 0.462
Present study.....	O.D. change in 30 minutes per 1.0 cc. serum	30	18.5	9.0 to 80.0	268 Normal	10.0	8.3 to 11.8
Disseminated.....		21	25.5	16.0 to 80.0	47 Misc.§	10.0	7.0 to 44.0
Localized and unclassified..		9	14.0	9.0 to 19.0			

*O.D. = Optical density.

†Zimmerman did not divide cases as to localized or metastatic.

‡Diphosphopyridine nucleotide (reduced).

§Miscellaneous controls were clinical states excluding carcinoma, myocardial disease, infectious mononucleosis, and liver disease (see Table 1).

vated amounts of lactic acid dehydrogenase in serum was first thought to be a reliable index of the presence of cancer and was so reported by B. Hill and others in 51 cases.² They found this enzyme to be increased in the serum and the amount to be significantly higher than in the serum of normal persons and patients with other clinical states, such as tuberculosis and pregnancy. However, Zimmerman reporting on 30 cases⁹ and J. H. Hill reporting on 87 cases,⁴ found only slight differences between patients with other illnesses and those with neoplastic diseases.

Our own observations in this field are summarized in Table 3 and comparison is made between the cases reported by other workers and those in our series. It is to be noted that division between metastatic and local involvement was not reported by all investigators. Our determinations indicated elevation of LDH in almost all patients with carcinoma. The mean was 18.5 units. In only five of these cases was the malignant lesion thought to be strictly localized, in 21 it was metastatic and in four cases unclassified. In the cases of dissemination as a group, the mean level was consistently elevated and showed a higher average (25.5 units) than the group as a whole. This is in agreement with the observations of McDonald.⁵

From our own observations we can conclude, with more certainty, that the lactic acid dehydrogenase level in serum will be elevated in most cases of metastatic carcinoma.

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Social Security Says:

"YOUR SOCIAL SECURITY TAXES pay for these nine programs: Social insurance: (a) Unemployment insurance; (b) Old Age and Survivors Insurance. Public assistance to the needy: (a) Old-age assistance; (b) Aid to the needy blind; (c) Aid to dependent children; (d) Aid to the permanently and totally disabled. Children's services: (a) Maternal and child health services; (b) Services for crippled children; (c) Child welfare services."

In other words: In spite of the fact that most of these represent federal grants to state aid, this Social Security program is being sold to you and me as "contributory social insurance."

—From the Department of Public Relations, American Medical Association